Force Generation and Shortening Capabilities of Left Ventricular Myocardium in Primary and Secondary Forms of Mitral Regurgitation

KEITH E. COHN, B. SHEILA RAO, AND JEROME A. G. RUSSELL

From the Departments of Cardiology and Research Data Facility, Presbyterian Hospital, Pacific Medical Center, San Francisco, California, U.S.A.

Differentiation between primary and secondary forms of mitral regurgitation poses a frequent and important clinical problem. In the *primary* variety of mitral incompetence, there is distortion of the valve leaflets, rupture or redundancy of the chordae tendineae, or papillary muscle rupture. Heart failure, if present at all in such cases, is assumed to be a consequence of the large regurgitant volume, and surgical correction of the mitral insufficiency, therefore, may result in clinical and haemodynamic improvement. *Secondary* mitral insufficiency is basically caused by myocardial dysfunction and left ventricular failure: dilatation of the left ventricle produces a malalignment of the papillary muscles, thereby leading to the valvular incompetency. The regurgitant volume is generally small in these instances, however, so that valve replacement is unlikely to be beneficial.

This study was undertaken in order to define those physiological features that merely reflect volume overload and those that reflect dominant muscle failure. Since primary mitral insufficiency and primary muscle dysfunction with secondary mitral incompetence both lead to severe disturbances in cardiovascular performance—the ventricular filling pressures may become raised, and the forward cardiac output considerably depressed in each group—it was apparent that some other means of assessing cardiac function should be investigated. One basic mode of characterizing myocardial function is expressed by the inverse relation between the force that a muscle develops and the velocity of shortening (Hill, 1938; Fry, Griggs, and Greenfield, 1964; Sonnenblick, 1962; Levine and Britman, 1964). In this paper, then, we have attempted to evaluate parameters that are related to muscle function *per se*—the extent and velocity of shortening and the force generation of the left ventricular myocardium.

SUBJECTS AND METHODS

The patients were classified as follows.

Group 1. Seven patients, ages 44 to 66 years, had *normal*, or at least near normal, left ventricular function. This group included 4 patients with mitral stenosis, all with resting left ventricular end-diastolic pressures below 12 mm. Hg; 1 patient with mild aortic stenosis; and 2 patients, initially evaluated because of chest pain, who were found to be normal by haemodynamic and coronary arteriographic criteria. While patients with mitral stenosis may have slight impairment in ventricular function, this was considered to be inconsequential for the purposes of this study.

Group 2. The 8 cases classified as having *primary mitral insufficiency* ranged in age from 26 to 72 years, and included 2 patients with chronic rheumatic mitral valve disease, 5 with ruptured chordae tendineae, and 1 with congenital mitral regurgitation. All but one of these cases had severe dyspnoea and pulmonary congestion, and 4 had right heart failure. Mitral valve replacement or repair was performed in 7 patients, and direct inspection of the valve at that time substantiated the impression of significant valvular incompetence. Five of these patients were symptomatically improved by the operation, returning to an active life; 2 died at operation.

Group 3. The group with *secondary mitral insufficiency* included 8 patients, 33 to 75 years of age, who appeared on the basis of several factors to have dominant myocardial dysfunction. Of these patients, there were 4 with coronary artery disease (3 with previous myocardial infarctions), 3 with cardiomyopathies, and 1 with hypertensive cardiovascular disease. All but

one of these patients had severe congestive failure clinically; the remaining one had had pulmonary oedema one month previously, but the signs and symptoms of left ventricular failure had regressed after medical management. In 4 of these patients the appearance of an apical systolic murmur several weeks to months after the appearance of cardiac decompensation was considered further evidence that only a secondary form of mitral insufficiency was present. One of the patients died, and at necropsy was proved to have severe coronary disease, with an old myocardial infarct and with slight valvular incompetence.

Right heart catheterization, generally with supine leg exercise, followed by retrograde arterial or transseptal left heart catheterization, was performed. The net (forward) cardiac output was determined by the direct Fick method, and intracardiac pressures were recorded through No. 7 fluid-filled catheters with P23 Db Statham pressure transducers on an Electronics for Medicine multichannel recorder.

Force and Shortening Measurements. Similar methods to those employed here have previously been applied in man to measure muscle shortening and tension, and were found to be reproducible and to be sensitive enough to detect at least moderate degrees of muscle dysfunction (Gault, Ross, and Braunwald, 1968).

Single-plane left ventricular cine-angiograms were obtained in the right anterior oblique projection, filming at 60 frames a second. 50 ml. 75 per cent Hypaque (sodium and meglumine diatrizoate) was injected into either the pulmonary artery, left atrium, or left ventricle. The left ventricular cavity silhouette and a portion of the left ventricular outer wall margin were traced onto tissue paper, frame by frame, using a Tage Arno projector. Though the right ventricle could potentially contribute to the wall thickness measured in the right anterior oblique view, Gault *et al.* (1968) have shown that this is not the case if traced at the mid-left ventricular level. Post-extrasystolic beats were excluded from the study. A 1 cm. square grid, placed at the level of the palpable left ventricular apex, was used for correction of spherical aberration and magnification.

The equipment used to obtain our data includes a Digital Equipment Corporation PDP-7 computer, a digitizer, and a cathode-ray tube display unit for presentation of original and derived haemodynamic and dimensional relations. The digitizing device is composed of two arms connected in series, as in a drafting machine or human upper extremity; the free end of one arm is moved over the pathway to be traced. A linear potentiometer at the "shoulder" generates a voltage proportional to the angle between the "humerus" and a reference axis on the tracing board, and a second potentiometer describes the angle between the upper and lower arms. These voltages are sampled by an analogue-to-digital converter under programme control. A sub-routine in the digitizing programme converts the two angular measurements into a first-quadrant rectangular co-ordinate system whose origin lies at the lower left-hand corner of the tracing board. The programme then stores a loci of points, and cal-

culates for each frame the longest cord and 100 equally spaced minor diameters passing through this cord. For simplicity of presentation only the minor diameters at 25 per cent of the distance from base to apex along the long cord are described here; results at the 50 per cent diameter were substantially the same. Before display all calculated data are smoothed with a three-point (33·4 msec.) running average. The programme will then print or graph on the cathode-ray tube any diameter length or shortening velocity as a function of time, extent of diameter shortening, tension as a function of time, or tension versus shortening velocity. "Velocity" is brought to normal by dividing by the instantaneous diameter, and is recorded in circumferences per second (circ./sec.).

A technician also records the angiographic frame number and corresponding left ventricular pressure, and these constitute input to the semi-automatic processing. Myocardial wall tension ("hoop stress", or force per unit area) was calculated by the equation PR/h, where P is the intracavity pressure in g./cm.^{2}, R is the radius to inner wall margin, and h is the left ventricular wall thickness, both in cm. Though this is the formula for the thin-walled cylinder, Popov (1952) has shown that it also represents the average tension across a thick-walled structure. The influence of longitudinal forces on the derived tension was not considered here.

Tensions were also estimated by two other equations: (1) that for a thick-walled cylinder

$$T = \frac{P\,R_i^2}{R_o^2 - R_i^2}\left(1 + \frac{R_o^2}{R_i^2}\right)$$

where R_i and R_o are the inner and outer wall radii (Popov, 1952; Sandler and Dodge, 1963) and (2) by employing a wall tension *index*, $T = PR$, which does not take wall thickness into account. These were compared in order to test the relative value of simple versus more complex estimations of tension.

Several possible sources of error should be considered. (1) The pressure measurements were made through fluid-filled Teflon catheters, and are, therefore, subject to some distortion and time lag depending on the frequency and phase response of the system. (2) The pressures at times were recorded before injection of contrast media, and on such occasions the pressures and cardiac dimensions were temporally related with the aid of a film marker and the electrocardiogram. Previous observations in this and other laboratories (Hallermann, Rastelli, and Swan, 1964) show that injection of contrast media changes the cardiac pressures and geometry slightly. (3) In order to minimize the potential error related to timing, the tensions at peak velocity were calculated both as a single, instantaneous value, and as a *range*. The latter was determined as the tension found 33·4 msec. (2/60 sec.) before and 33·4 msec. after the instant of peak velocity. (4) The velocity of contractile fibre shortening (V_{CF}) does not specifically reflect myocardial function, and contractile element velocity (V_{CE}) (Hill, 1938; Levine and Britman, 1964), a more meaningful parameter, was not determined.

V_{CE} is equivalent to V_{CF} only at peak tension (when the first derivative of tension becomes zero), but in view of the uncertainties regarding exact timing and pressure measurements we hesitate to present this figure. During ejection and before peak tension is attained, V_{CE} and V_{CF} are comparable, however (Ross, Covell, and Sonnenblick, 1967). (5) Finally, it should be emphasized that other variables known to influence the myocardial force-velocity relations, such as instantaneous fibre length, heart rate, inotropic environment, and series elastic component stiffness (Hill, 1938; Fry et al., 1964; Sonnenblick, 1962; Levine and Britman, 1964; Ross et al., 1967; Sonnenblick, 1964) were not specifically considered. These potential errors were tolerated since one aim of this study was to develop a relatively simple and generally applicable technique for assessing ventricular function. Since a micromanometer-tipped catheter was not available to us, and since routine placement of two catheters into the left ventricle is impractical, we accepted several compromises with the expectation that the errors would not nullify the overall value of the study.

RESULTS

Net Cardiovascular Performance. Of the 8 patients with primary mitral insufficiency, 7 had marked abnormalities in cardiovascular performance, manifested by high ventricular filling pressures or low forward flows. Six had low resting forward cardiac indices (less than 2·5 l./min. per m.²) and 7 had inappropriately small increases in output with exercise (an "exercise factor" of less than 500 ml./min. cardiac output rise per 100 ml./min. increase in oxygen consumption). Five of these patients also had resting left ventricular end-diastolic pressures (LVEDP) greater than 12 mm. Hg. Only one of the patients with mitral insufficiency displayed near normal "performance", she being the patient without symptoms.

Of the 8 patients with secondary mitral regurgitation, 7 were found to have severe impairment of net cardiovascular performance, with resting cardiac indices below 2·5 l./min. per m.² in 4, low exercise factor in 4 of 5 tested, and raised LVED pressures in 7 patients.

All patients from Group 1 (those with normal left ventricular dynamics) had LVED pressures below 12 mm. Hg at rest. The 3 patients without mitral stenosis also had normal pulmonary artery wedge pressures during exercise, as well as normal resting and exercise cardiac outputs. The patients with mitral stenosis had low exercise factors and high pulmonary artery wedge pressures, due to the obstructing orifice.

Force and Shortening Parameters. The Table shows the diameters at end-systole and end-diastole, the extent and velocity of diameter shortening, and

TABLE
FORCE AND SHORTENING

	Normal	Primary mitral regurgitation	Secondary mitral regurgitation
End-diastolic diameter (cm.)			
Range	7·3—5·1	10·7—6·2	9·1—6·1
Mean	6·1 ± 0·3	8·4 ± 0·6	7·6 ± 0·4
End-systolic diameter (cm.)			
Range	5·2—2·9	8·2—3·8	8·3—4·1
Mean	3·8 ± 0·3	5·6 ± 4·9	6·6 ± 0·4
Extent of diameter shortening (cm.)			
Range	1·7—3·4	2·0—4·1	0·4—2·1
Mean	2·1 ± 0·2	2·8 ± 0·3	1·0 ± 0·2
Extent of diameter shortening (%)			
Range	31—53	25—44	7—34
Mean	37 ± 2·7	35 ± 2·3	13 ± 3·0
Peak velocity of fibre shortening (circ./sec.)			
Range	1·7—4·0	1·5—3·5	0·6—2·2
Average	2·8 ± 0·3	2·4 ± 0·3	1·0 ± 0·2
Peak tension (g./cm.²)			
Range	170—450	180—750	200—500
Mean	284 ± 34	350 ± 60	357 ± 41

± = Standard error of the mean.

the peak developed tension. In primary mitral insufficiency, the diastolic diameters were significantly greater than normal (p < 0·01; Fig. 1), but the extent of diameter shortening, expressed either as a dimension or as a percentage change, was not significantly different from normal. The group with secondary mitral regurgitation demonstrated large diastolic diameters, similar to those of the primary mitral regurgitation group (Fig. 1), but showed an average extent of diameter shortening which was significantly depressed as contrasted with Groups 1 and 2 (p < 0·01; Fig. 1).

The average tensions generated at peak velocity were not significantly different in Groups 2 or 3 compared with Group 1, but 2 patients with primary mitral incompetence developed tensions of 500 g./cm.² or above, values greater than those seen in the normal group.

The linear correlation between the tensions calculated by the equation PR/h and by the thick-walled cylinder equation was 0·97.* The formula "PR" correlated less well with PR/h (r = 0·77).†

There was no significant difference between the average peak velocities of fibre shortening (V_{CF})

* Regression equation: $\dfrac{P\,R_i^2}{R_o^2 + R_i^2}\left(1 + \dfrac{R_o^2}{R_i^2}\right) = 1·06\,PR/h + 91.$

† Regression equation: $PR = 0·92\,PR/h + 124.$

found in the normal and primary mitral insufficiency group. Six of the patients with primary mitral regurgitation had V_{CF}'s within the range seen in the normal group, and in 2, the V_{CF} was borderline but probably normal (1·5 and 1·6 circ./sec.). Six of the patients with secondary mitral incompetence had diminished peak velocities of fibre shortening (0·6 to 0·8 circ./sec.) and only 2 had V_{CF} in the normal or borderline range (1·6 and 2·2 circ./sec.). The mean V_{CF} of the entire group was $1·0 \pm 0·2$ circ./sec., significantly lower than that found in the normal and primary mitral incompetency patients (p < 0·01). Of the 2 patients with essentially normal contractile fibre velocities, one had pulmonary oedema one month previously, but by the time of study had attained near normal cardiac compensation with normal resting and exercise forward flows and only slight increases in LVEDP (14 mm. Hg). The other patient had a large ventricular aneurysm at the cardiac apex and it was the basal portion of the heart which displayed a near normal V_{CF}. He subsequently showed clinical improvement after surgical removal of the aneurysm. The relation between the tension, expressed as a range (see above), and velocity is graphed in Fig. 2.

DISCUSSION

The patients with primary and secondary mitral insufficiency had severe degrees of impairment in cardiovascular performance. In both groups the resting and exercise cardiac outputs were depressed and the ventricular filling pressures were raised. Tall left atrial V waves were frequently evident in both groups, confirming the well-known observation that left atrial pressure and contour are as much an indication of wall compliance as of regurgitant volume (Braunwald and Awe, 1963). The main features distinguishing these two classes of patients, then, seemed to be the myocardial shortening capabilities of the left ventricle. The patients with primary mitral insufficiency had normal extents of fibre shortening and contractile fibre shortening velocities in the "normal" or low normal range (see below). In the patients with dominant myocardial disease and secondary mitral regurgitation these parameters were very depressed. Thus, the muscle appears to perform in a near normal fashion in the primary mitral regurgitation group.

These findings are in accord with several previous observations. Ross *et al.* (1967) have studied an experimental form of acute cardiac failure and have noted a decrease in the extent of fibre shortening and a diminution of fibre shortening velocity (V_{CF}) and contractile element velocity (V_{CE}) com
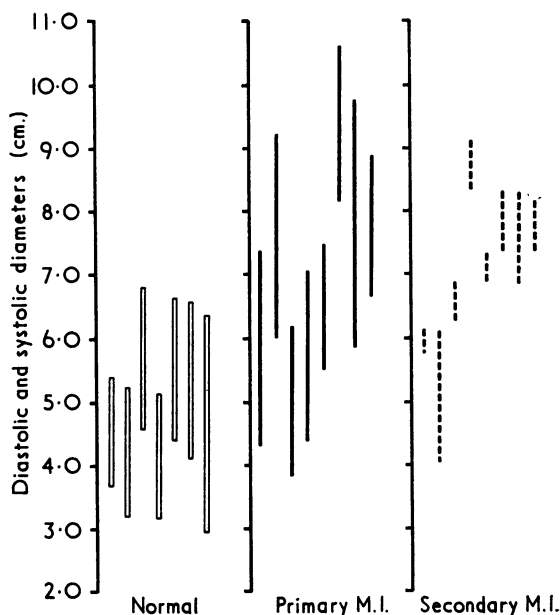

FIG. 1.—The ends of each vertical bar define the end-diastolic and end-systolic minor diameter length measured at 25 per cent of the distance from base to apex. The length of each bar thus shows the extent of diameter shortening.

pared with normal. Gault *et al.* (1968) have made similar observations in patients with dominant myocardial disease. Other groups (Bunnell, Grant, and Greene, 1965; Hood *et al.*, 1967) have reported a normal ejection fraction (EF = stroke volume/end diastolic volume) in cases of mitral regurgitation, reflecting a normal extent of fibre shortening. Though such findings are most usual in primary
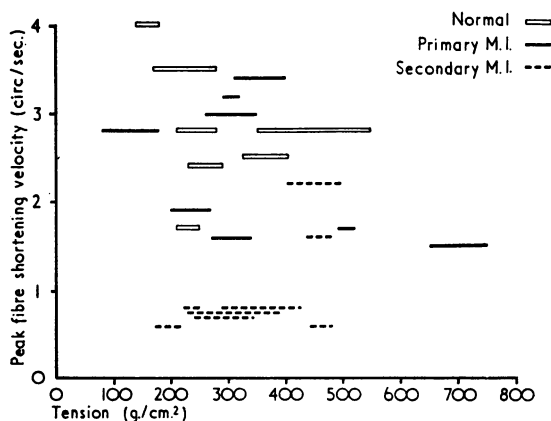

FIG. 2.—Peak contractile fibre velocity (in circumferences/second) is plotted against the corresponding tension (in g./cm.²). The tension is expressed as a range in order to minimize timing errors (see "methods" section).

mitral insufficiency, a decreased ejection fraction in several instances of mitral insufficiency has been detected and attributed to a depressed level of myocardial contractility (Miller, Kirklin, and Swan, 1965; Jones *et al.*, 1964). It should be pointed out, however, that the ejection fraction does not necessarily indicate the contractile state of the myocardium, since it is also influenced by both the end-diastolic volume and the resistance encountered during left ventricular ejection (Tsakiris *et al.*, 1966; Urschel *et al.*, 1968).

The myocardial wall tensions were most commonly normal in the patients with primary and secondary mitral insufficiency, though individual cases from both groups developed high peak tensions. If myocardial hypertrophy develops proportionately with ventricular dilatation, the ratio of wall-thickness to chamber diameter will remain essentially normal (Grant, Greene, and Bunnell, 1965). Presumably such hearts will generate normal wall forces in spite of their dilatation. Normal wall tensions have, in fact, been noted in cases with primary myocardial disease and even in cases with severe aortic stenosis (Gault *et al.*, 1968; Sandler and Dodge, 1963). In volume overload states, such as mitral insufficiency, the hypertrophy probably fails at times to increase commensurately with the dilatation, and, therefore, wall stresses are seen to range from normal to slightly raised (Sandler and Dodge, 1963; Hood *et al.*, 1967).

The close correlation between PR/h and the equation for a thick-walled cylinder indicates that there is little advantage in employing the latter potentially more laborious means of assessing wall tensions. While the tension index, PR, correlated less well, it did provide a fair estimate of tension, and might well be used in some studies where wall thickness cannot be measured.

We can propose several reasons to explain the normal or near-normal shortening capabilities of the left ventricular myocardium in primary mitral insufficiency. The first is that these patients do not have typical heart failure, and, therefore, may not in many instances have depressed myocardial contractile function at all. Mitral insufficiency is a form of "high-output failure", the stroke volume being significantly increased over the normal. In the presence of severe regurgitation, the muscle must perform well in order to deliver an adequate blood supply to the tissues. Marked depression of muscle function, to the degree observed in advanced primary myocardial disease, would, in effect, be incompatible with life.

Another explanation for the findings is the possibility that the observed velocities of fibre shorten-

ing are not normal at all. Urschel *et al.* (1968) have studied acute mitral insufficiency under controlled experimental conditions, and have noted both supernormal extents of fibre shortening and increases in V_{CF} and V_{CE}. They attributed these findings to the *low impedance* to left ventricular emptying, the left atrium acting as a low resistance conduit in parallel with the systemic circuit (Urschel *et al.*, 1968). They also speculated that a positive feedback mechanism might be acting: as systole progressed the regurgitation allowed a rapid diminution in minor diameter, thereby evoking a more rapid than normal decrement in tension. Since velocity and extent of shortening are each reciprocally related to afterload (Urschel *et al.*, 1968), a rapid diminution in tension might well contribute to the augmented shortening extents and velocities. Thus, the velocities observed in some of our cases might actually be slightly depressed from what would be expected if normal muscle were subjected to mitral reflux, and the findings may reflect early muscle failure.

A disparity between the degree of impairment of net cardiovascular performance and degree of muscle failure is evident in this study. Since muscle function need not correlate with the clinical or haemodynamic findings, we suggest a redefinition of terms in order to clarify the various types of "heart failure" observed. "Circulatory congestion" (Eichna, 1960) would indicate the presence of increased cardiac filling pressures, at times associated with high blood volume, peripheral or pulmonary oedema, or serious effusions; this classically occurs in acute glomerulonephritis. Decreased "net cardiovascular performance" could imply, in addition to the congestive signs, a low forward cardiac output; aortic or mitral insufficiency, and mitral stenosis are examples. If "depressed myocardial contractility" were present as well, the force and shortening capabilities of the muscle would then appear abnormal: this could occur in primary myocardial disease, coronary artery disease, or might develop as a result of severe or prolonged valvular stenosis or insufficiency.

It is not anticipated that the distinction between primary and secondary mitral insufficiency will always be as clear as noted here, since the cases selected for this study represented the most clinically obvious ends of a spectrum. It is reasonable to assume, for example, that patients with dominant myocardial dysfunction of less severity will have force-velocity-shortening relations more near normal. Patients with coronary artery disease would be expected to present especially complex examples of over-all muscle function, since there are varying

degrees of damaged or ischaemic myocardium within a heart (Herman *et al.*, 1967), and since papillary muscle dysfunction (Burch, De Pasquale, and Phillips, 1963) may lead to an added element of mitral insufficiency.

SUMMARY

A means of differentiating primary mitral insufficiency (due to intrinsic valvular disease or prolapse) from secondary mitral insufficiency (due to ventricular failure) was sought. Cardiac catheterization data and cine-angiograms were obtained on 7 patients with normal left ventricular function, 8 with primary mitral insufficiency, and 8 with secondary mitral insufficiency. The normals developed peak fibre shortening velocities (V_{CF}) from 1·7–4·0 circumferences per second, and the minor diameter shortened an average of 2·1 cm. In 6 cases of primary mitral insufficiency, V_{CF} was normal (1·7–3·4 circ./sec.), and in 2 V_{CF} was borderline (1·5 and 1·6 circ./sec.). These patients developed normal to moderately increased wall tensions at peak V_{CF}, and all had normal extent of diameter shortening (av. 2·8 cm.). Patients with secondary mitral insufficiency had diminution in extent of diameter shortening (av. 1·0 cm.) and maximum V_{CF} (av. 1·0 circ./sec.).

We conclude that patients with primary mitral insufficiency demonstrate near normal force generation and shortening capacities due to essentially normal myocardial contractility and to low resistance to ejection, and can be distinguished from cases of secondary mitral insufficiency.

REFERENCES

Braunwald, E., and Awe, W. C. (1963). The syndrome of severe mitral regurgitation with normal left atrial pressure. *Circulation*, **27**, 29.

Bunnell, I. L., Grant, C., and Greene, D. G. (1965). Left ventricular function derived from the pressure-volume diagram. *Amer. J. Med.*, **39**, 881.

Burch, G. E., De Pasquale, N. P., and Phillips, J. H. (1963). Clinical manifestations of papillary muscle dysfunction. *Arch. intern. Med.*, **112**, 112.

Eichna, L. W. (1960). Circulatory congestion and heart failure. *Circulation*, **22**, 864.

Fry, D. L., Griggs, D. M., Jr., and Greenfield, J. C., Jr. (1964). Myocardial mechanics: Tension-velocity-length relationships of heart muscle. *Circulat. Res.*, **14**, 73.

Gault, J. H., Ross, J., Jr., and Braunwald, E. (1968). Contractile state of the left ventricle in man: Instantaneous tension-velocity-length relations in patients with and without disease of the left ventricular myocardium. *Circulat. Res.*, **22**, 451.

Grant, C., Greene, D. G., and Bunnell, I. L. (1965). Left ventricular enlargement and hypertrophy. A clinical and angiocardiographic study. *Amer. J. Med.*, **39**, 895.

Hallermann, F. J., Rastelli, G. C., and Swan, H. J. C. (1964). Effects of rapid injection of heparinized blood into right and left ventricles in dogs. *Radiology*, **83**, 647.

Herman, M. V., Heinle, R. A., Klein, M. D., and Gorlin, R. (1967). Localized disorders in myocardial contraction. Asynergy and its role in congestive heart failure. *New Engl. J. Med.*, **277**, 222.

Hill, A. V. (1938). The heat of shortening and the dynamic constants of muscle. *Proc. roy. Soc. B*, **126**, 136.

Hood, W. P., Rackley, C. E., Rolett, E. L., and Young, D. T. (1967). Relationship between wall stress and chamber size in the hypertrophied human left ventricle. *Circulation*, **36**, Suppl. 2, p. 144. (Abstract.)

Jones, J. W., Rackley, C. E., Bruce, R. A., Dodge, H. T., Cobb, L. A., and Sandler, H. (1964). Left ventricular volumes in valvular heart disease. *Circulation*, **29**, 887.

Levine, H. J., and Britman, N. A. (1964). Force-velocity relations in the intact dog heart. *J. clin. Invest.*, **43**, 1383.

Miller, G. A. H., Kirklin, J. W., and Swan, H. J. C. (1965). Myocardial function and left ventricular volumes in acquired valvular insufficiency. *Circulation*, **31**, 374.

Popov, E. P. (1952). *Mechanics of Materials*, pp. 419–420. Prentice-Hall, New York.

Ross, J., Jr., Covell, J. W., and Sonnenblick, E. H. (1967). The mechanics of left ventricular contraction in acute experimental cardiac failure. *J. clin. Invest.*, **46**, 299.

Sandler, H., and Dodge, H. T. (1963). Left ventricular tension and stress in man. *Circulat. Res.*, **13**, 91.

Sonnenblick, E. H. (1962). Implications of muscle mechanics in the heart. *Fed. Proc.*, **21**, 975.

—— (1964). Series elastic and contractile elements in heart muscle: Changes in muscle length. *Amer. J. Physiol.*, **207**, 1330.

Tsakiris, A. G., Banchero, N., Sturm, R. E., and Wood, E. H. (1966). Inverse relationship between end-diastolic volume and ejection fraction of the left ventricle. (Abstract.) *Circulation*, **34**, Suppl. 3, p. 230.

Urschel, C. W., Covell, J. W., Sonnenblick, E. H., Ross, J., Jr., and Braunwald, E. (1968). Myocardial mechanics in aortic and mitral valvular regurgitation: The concept of instantaneous impedance as a determinant of the performance of the intact heart. *J. clin. Invest.*, **47**, 867.